patients you studied with motility to evaluate that problem?

DR. O'BRIEN: Very few in my series. This is a personal series, not any part of the study. There were none, no motilities above that. I've studied now about 15 patients at 12 months, a larger number before operation were done follow-up motility in these patients at 12 months and we have not identified any dismotility in those patients.

DR. SAWICKI: But they did have dilated esophaguses?

DR. O'BRIEN: No, no, no, no, the dilatation that was quite familiar, reported earlier today, mentioned the enlargement of the esophagus from 2.2 centimeters to 3.3 centimeters. Our radiologists don't regard that as dilated.

DR. SAWICKI: Fair enough, thank you.

DR. KALLOO: Okay.

DR. MacDONALD: Just to briefly cover a couple of those questions that show the band-related adverse events by site. The middle column is band slippage, pouch dilatation. The last column is stoma obstruction. You can see that, percentage-wise, there was some variation in centers and for stoma obstruction, there was a rather wide variation between centers. Now, this just looks at those two band-related adverse events. We could find it for others, I'm sure.

Lost to follow-up, the figure I'm given is 12 total patients of 299 or four percent were lost to follow-

up. There are some remaining where there is no data at 36 plus or minus three months. So, that wasn't defined as lost follow-up, but maybe some of them will be included.

I'm going to finally discuss the risk-benefit conclusions presentation.

The risks associated with LAP-BAND, as I see it, are general operative risks and risks of anesthesia, stoma stenosis or obstruction, band slippage, band erosion, GE reflux and the risk, of course, of reoperation or explantation. Again, these have to be considered, I think, with the known risks of other procedures as gastric bypass and vertical banding gastroplasty as well as the risk of continued untreated morbid obesity.

These are non-benefits, the minimally invasive technique just mentioned, because this is a device that was designed to be put in laparoscopically. There is reduced wound complications, including hernias. Both Dr. Sugarman and myself reported 25 percent incidence of incisional hernias with the gastric bypass surgery. There is lower morbidity and mortality in peri-operative, important reduced postoperative pulmonary problems. That is a very big benefit in the morbidly obese, where pulmonary problems after surgery are very common.

There is reduce postoperative pain, reduced intra-abdominal adhesions or scar tissue which facilitates future

surgery if necessary for any reason. Possibly we will reduce the future incidence of adhesive bowel obstructions, which is the most common cause of bowel obstructions now in this country.

There is a short hospitalization, faster return to normal activity and to work. Again, related to the adhesion issue, it allows laparoscopic revisions and the revisions necessary for any of the common operations.

Finally, there is increase patient and referring physician acceptances, which makes these operations available to more people who need them. There is no question we have seen increased referrals for obesity surgery, which I think is key.

From data presented, the benefits of the LAP-BAND system are significant and sustained weight loss, improvement in comorbidity, particularly as shown in the international results, significant improvement in quality of life, the ease of laparoscopic placement and the ability to reverse laparoscopically, in many cases. Importantly, the band is able to be non-invasively adjusted according to nutritional needs or therapeutic needs, whatever, just by placing a needle in it and putting in or withdrawing saline.

The risk of major, serious peri-operative complications are reduced. Finally, as was mentioned by one of the patient talks, you avoid staple lines and anastomoses

and bypass of the GI tract, which keeps a lot of patients away from surgical treatment.

The band is not meant to replace the surgical alternatives, the gastric bypass or VBG. I definitely have a long term bias for gastric bypass. It does fill an available gap between these more invasive operations and medical management.

So, I would leave that, this U.S. study results as well as the international and the meta-analysis results supports the safety and efficacy of the LAP-BAND for its intended use, as was detailed here in a previous slide.

I will next have Ellen Duke, President and CEO, complete the presentation with the discussion of--

DR. LINNER: I have a question.

DR. MacDONALD: Yes, sir.

DR. LINNER: Could you tell us how long one of these procedures requires, the entire procedure, say, in a beginning part of the training and then later on, is there any more morbidity with the increased CO_2 pressure, abdominal pressure during the course of surgery?

DR. MacDONALD: Just speaking personally, our first ones probably took three hours. Not being a particular whiz at laparoscopy, that has gone down to under two hours. Dr. Paul O'Brien, who has done many more, can do it in under an hour. So, there is a distinct decrease in

the time required.

I do not know of any CO_2 problems. Of course, with the shorter operation in such, I don't think you will see any more with this than with, say, a laparoscopic Nissen, even though, of course, with the morbidly obese, you have to use higher insufflation pressures often times to see better. I really don't recall seeing an increased problem.

DR. LINNER: Okay.

DR. MacDONALD: Yes, sir?

DR. BARANSKI: Were there any persistent findings at the time of reoperation for the slippage that you found?

DR. MacDONALD: Persistent findings would include a posterior gastric wall that was free of any adhesions to tether it. I believe--this is completely personally--that there needs to be a modification in technique where you fix that posterior gastric wall in every patient or, at least, look at it to see if it needs fixed. So, you're not force to put the band too high.

If you put the band right at the GE junction, you're going to get this esophageal dilatation problem much more often, because you have a band around the esophagus. If you have a proximal gastric pouch, you shouldn't have any more obstruction than you do after most of the other restrictive operations and should not see an increased incidence of that.

Anyway, that posterior gastric wall can easily be visualized by a couple of different approaches. You can pull the stomach down through the band and then just put in those necessary two or three sutures.

DR. BARANSKI: Did you find that the anterior sutures slipped on any of them?

DR. MacDONALD: I did not. I have not found on four or five reoperations for slippage any problems with the anterior stomach.

DR. TALAMINI: I have a clarification as well. I know it wasn't in the analysis of the data, but there is quite a bit of variability in success with this device. Is there any hint in the date from your analysis--I know there is no formal analysis--as to who will do well with this device and who not so well?

DR. MacDONALD: That's a huge question with any gastric restrictive operation for obesity. There's everything from personality types and many numerous physiologic factors, race, sex, the weight you start out with. So many things affect the amount of weight loss from these operations.

The data we have, unfortunately, don't point to any one thing that you could use. There are not, I don't think, any conclusions. I know any of us who do this surgery have some pretty definite opinions about who has a

better chance of doing well. We try our best to appropriately select patients, but that requires a lot of experience and, in most cases, I think a lot of luck.

DR. GABRIL: How can you determine whether the dilatation of the pouch is secondary to the slippage of the stomach or chronic distension from the stoma itself?

DR. MacDONALD: We can't. That's why it was included together in most cases with the analysis. You really couldn't tell whether the dilatation was just simply the pouch stretching some or whether it was actually slippage. I personally think in a lot of cases, it was a degree of slippage in all pouch dilatations.

MS. NEWMAN: I'm interested too in the differences in the identification of patients because it seems like the European data, the patients were not as super obese. Again, you don't have any information on those previous patients where each one of you did 50. Did you change your criteria for selection when you went into the study? It would be really interesting to note that and may also indicate why we have differences in this country.

That is really important, because if this is approved, people are just going to come forward and the issue of selection doesn't become as important as what people want in this country.

DR. O'BRIEN: I don't believe there was any change

in the selection criteria of the surgeons, but we have measured the impact of potential selection criteria on outcomes, such as age, such as sex, such as initial weight. We can notice differences between groups, particularly in relation to initial weight. The higher the weight is initially, the less effective in terms of percent of excess weight loss the outcome will be.

Nevertheless, there have been important benefits. We have not identified any groups whose benefit drops down so low that we feel that it hasn't been clinically worthwhile. So, I haven't identified a subgroup who we say we should exclude. We have only started treating people at the BMI of 35 or upwards, and generally almost invariably they've had comorbidities associated with it. That remains, I think, a strong basis for selection of patients. We are not recommending any change from that selection criteria.

DR. CHOBAN: I have a question for Dr. MacDonald. In terms of sort of coming back to the selection and the appropriate candidates for this, in looking at the international data and the improvement in diabetes, with resolution at only 40 percent is very different than what has been reported with your institution with gastric bypass.

So, in the subset of diabetics, is the lower efficacy in resolution an issue to you?

DR. MacDONALD: It would be an issue if the data

on comparison bore themselves out in that fashion. It would be an issue.

DR. O'BRIEN: I can comment on that in my own data; that the diabetics do less well, but they still do well. In my personal series, where the average weight loss is 55 percent of excess weight, the diabetics on average lose 47 percent of excess weight. So, it seems for some reason less effective in that group.

The follow-up data that was asked for before, there are 25 patients. So, 21 patients have been lost to follow-up in that follow-up period.

DR. HIRSCH: Out of the 441, only--what was the number?

DR. O'BRIEN: Twenty-one.

DR. HIRSCH: Twenty-one, thank you.

DR. SAWICKI: One more question, in your inclusion in and exclusion criteria for the study, do patients on chronic steroids fit into either category?

DR. MacDONALD: Do patients on steroids affect the inclusion or exclusion criteria?

I do not know. I don't believe so, no.

DR. SAWICKI: Thank you.

DR. FOOTE: I have one quick question for both surgeons. Given the relatively high incidence of slippage, why was not the institution of routinely placing posterior

sutures not done?

DR. MacDONALD: I can answer first.

Again, the U.S. study never really got much above the learning curve with each particular center. So, this was a problem in evolution. So, by the time that the study, the accrual end of the study occurred or stopped, we still didn't have a total idea of the severity of the problem. A lot of these are presented in a year. Most of mine actually waited 11 to 12 months to present. So, they didn't start presenting until accrual had already been stopped or was near stopping. So, that's why there was no change in technique.

DR. LINNER: I have a question relative to the suturing posteriorly as well as anteriorly. Do you think that will increase the incidence of the erosion of the band?

DR. MacDONALD: That's a good question, obviously, because of our past experience with bands and such. That is an obvious concern that, in the international study, has not been borne out yet after four to six years. We only had three band erosions, two of which were due to, I'm sure, an intraoperative injury which is (?) and a band placed over it.

So, that is something that obviously has to be watched for with continuing follow-up, which is necessary, as you know, John, with any of our gastric restrictive

operations.

DR. LINNER: One more question. Did anyone besides the group, the Medical College of Virginia, do esophageal studies in these groups routinely, not waiting for symptoms but trying to determine whether the esophagus had dilated, in fact, besides the University of Virginia?

DR. MacDONALD: Medical College of Virginia.

DR. LINNER: Yes, sorry.

DR. MacDONALD: Dr. Greenstein did some studies involving hiatal hernia and such. So, he did do a lot of manometries, endoscopies and upper GIs. I do not know the results of those specifically. They are presuming that--by and large, I don't know that anybody else did them outside of the study unless there were symptoms for the usual scheduled examinations obtained at regular follow-up periods. There is not a lot of manometry data that I know of.

DR. KALLOO: Unless there are other questions, let's--

DR. GABRIL: I was thinking about the quick weight loss that was seen at 18 to 24 months and then it stabilized. Do you have an explanation for that?

DR. MacDONALD: To correlate with mine and others' experience, say, with a gastric bypass, it's almost like clockwork the patients will maximize their weight loss at

somewhere between one and two years and then remain relatively stable for a year or two. Some will regain up to a nine percent mean of that lost weight and then it stays pretty stable on out in our series to 16, 17 years.

So, that seems to be the natural trend with restrictive or even malabsorptive operations. Once the weight loss stabilizes at this new plateau, then it tends to be stable and what you fear, of course, is weight regain. It is very rare for it to keep going too low.

DR. KALLOO: Go ahead.

MS. NEWMAN: The people that gained the band who really don't see that success, have you analyzed any of that data, to look at characteristics of that population that could in any way impact on your selection criteria for people for this surgery?

DR. MacDONALD: No, ma'am, I have not.

MS. NEWMAN: Has the company done any of that? It sounds like the company internationally has a tremendous amount of data out there, especially if you guys did 50 before you even went into a study.

DR. MacDONALD: That's obviously a hugely key issue.

DR. KALLOO: Okay, I would like to move on to the final presentation, please.

MS. DUKE: BioEnterics has recognized that the

potential benefits of the LAP-BAND system attract great interest in the United States, as they have internationally. With this interest comes responsibility.

Our labeling and training plans are designed to support the surgeons and the FDA's efforts to provide the best possible health care to American patients. Accordingly, our proposed labeling is in compliance with the joint guidelines for surgical treatment of morbid obesity, developed by the American Society for Bariatrics Surgery end stages and notes that, surgeons should have advanced laparoscopic skills, experience or training in bariatrics surgery, the appropriate support staff and facilities for long term patient support and a commitment to do enough procedures with enough frequency to move through the learning curve in both placement and patient management.

Participation in a company-authorized workshop is required as well as OR staff in-services regarding preparation and handling and proctoring by an experienced surgeon.

The training workshops are designed to provide the surgeon with the information needed to do the procedure and, just as important, to make clear what we cannot provide, but come only from the surgeon, the skills, the experience and the training, the staff and the commitment to long term care of this patient group.

The workshops include lectures, discussion, labs, surgery demonstration and a workbook and are facilitated by surgeons with significant experience with the procedure and patient management.

This is a list of the multicenter clinical studies that BioEnterics is sponsoring and proposes to complete as a part of a voluntary post-market program. This is all a part of BioEnterics Corporation's commitment to our customers, the surgeons and also to our ultimate customers, the patients who utilize the LAP-BAND system as a tool to change their lives for the better.

As you can see, this involves four separate studies, involving over 1,000 patients, the majority being followed for three or more years.

We hope that you agree that the LAP-BAND system represents a safe and effective option for the treatment of severe obesity and fills the gap between medical therapy and the more invasive surgical alternatives.

Thank you very much.

DR. KALLOO: Okay, thank you.

We will reconvene at 1:30 after a short lunch break.

Thank you.

[Whereupon, there was a luncheon recess.]

A F T E R N O O N S E S S I O N

[1:32 p.m.]

DR. KALLOO: This meeting will get started in a few seconds if everyone can please take their seats, who are standing.

[Pause]

DR. KALLOO: This meeting will be reconvened with the FDA portion of the open committee discussion. I would like to remind the panel that they may ask for clarification of any points included in the presentation. Discussion should not go beyond clarification.

The first speaker for the FDA is Kathleen Olvey.

PRESENTATION OF

KATHLEEN OLVEY, BIOLOGIST GRDB

MS. OLVEY: Good afternoon.

I'm Kathleen Olvey. I'm going to give a review of the PMA submitted by--

DR. KALLOO: We can't hear you. I'm sorry. You're not turned on.

[Pause]

MS. OLVEY: Good afternoon.

My name is Kathy Olvey. I'm the lead reviewer for the PMA submitted by BioEnterics Corporation for the LAP-BAND, adjustable banding system. This PMA was received on February 7th of this year.

Reviewers from several offices within the center analyzed the data in this submission. In addition to my review, data related to the non-clinical performance of the device was reviewed by Gema Gonzalez. The clinical data were reviewed by Dr. Brian Harvey and Dr. Gene Pennello.

Patient labeling was reviewed by Mary Ann Wollerton from the Office of Health and Industry Programs. Sharon Ellerbe and the Office of Compliance has reviewed the manufacturing information. That office determined that, because the sponsor was inspected during a pilot program in 1999, a pre-approval inspection would not be necessary.

Barbara Crowl from the Office of Compliance, by a research monitoring, is coordinating the site visits with the field offices to review the patient data at several investigational sites.

My presentation will be an overview of the pre-clinical studies conducted by the sponsor and the other FDA presentations will focus on the clinical data.

As proposed by the sponsor, the LAP-BAND is indicated for use in severely obese adult patients. These patients have a BMI of at least 40, a BMI of 35 with at least one severe comorbidity or they are at least 100 pounds over their ideal weight. Patients can be considered for implantation if they have failed more conservative weight alternatives, such as, supervised diet, exercise and

behavior modification programs.

Patients who elect to undergo this surgery, must make a commitment to life changes in diet and behavioral modifications.

As previously described the sponsor, the implantable components of the LAP-BAND system are the silicon elastomer band, an access port and kink-resistant tubing used to connect the two components. All three of these components are considered permanent implants. The gastric band's slip-through buckle facilitates laparoscopic placement around the stomach. The inner surface of the gastric band is inflatable. This inflatable surface is connected by the tubing to the access port.

The access port has a self-sealing injection site and is designed to allow for postoperative percutaneous adjustments in the stoma diameter. The gastric band is usually placed in a laparoscopic procedure, but it can also be placed during a laparotomy. After placement of the gastric band, the band tubing is brought outside of the abdomen and attached to the access port.

The port is positioned in the rectus muscle and then sutured in place. Placement of the band around the stomach creates a small gastric pouch and a restricted opening for stoma. This is done to limit food consumption and induce early satiety.

Unlike other bariatrics surgical procedures, the access port in the LAP-BAND system allows for post-surgical modification at the stoma size. Removing saline from the inflatable inner surface of the band, through the access port results in a loosening of the band an increases the size of stoma. This can done if the subject is experiencing certain adverse events such as stoma obstruction or band slippage. Increasing the size of the stoma is also recommended for subjects who become pregnant after placement of the LAP-BAND to allow for increased nutritional needs.

In subjects who are not losing weight, the size of the stoma can be reduced by the addition of saline through the access port.

The review of the pre-clinical studies included evaluation of the results of testing done on the materials, on device performance and on the sterilization method. Pre-clinical studies were conducted on the raw materials used to fabricate the device, the components from which the device is assembled, the finished device and the device packaging and sterilization process.

The LAP-BAND is a permanent implant. All patient contacting materials underwent biocompatibility testing. Testing was conducted on both the raw materials and on the finished, sterilized device. Titanium and stainless steel have been excessively used in medical devices. Testing on

the unprocessed silicon elastomer was conducted by the materials manufacturers, in accordance with the FDA's guidance of manufacturers of silicon devices, affected by the withdrawal of Dow-Corning's elastic materials.

Testing on the finished device was conducted by the sponsor, following the guidance ISO 10993-1 by a Logical Evaluation of Medical Devices, Part I, Guidance on Selection of Tests. All testing was carried out in compliance with good laboratory practice regulations.

The materials used in the sterilized, finished device pass all the biocompatibility testing. In addition, there were no reports of material-related adverse events during the clinical trial.

Performance testing was conducted to evaluate all levels of the manufacturing process, raw materials, components and finished device. The tests that were conducted included device insertion testing, to evaluate performance during laparoscopic placement. Device inflation testing validated shell component integrity. Tensile testing evaluated the forces necessary to separate component bonds and connections. A tubing and access port testing evaluated the performance of these components of the LAP-BAND system.

The results from all of the tests demonstrated that the finished device meets the sponsor's acceptance

criteria for each of the tests. Also, the design of many of the tests were such that, the device or the component were subjected to conditions exceeding those expected during clinical use. So, the device was actually tested to failure or to conditions beyond working parameters.

During the clinical study, there have been several reports of device malfunctions, most associated with the access port or the access port tubing. There were two reports of the LAP-BAND system developing leaks. In these two cases, the entire system was removed without replacement with a new LAP-BAND system.

Like I already mentioned, most of the reported malfunctions were associated with the access port. There were a total of 20 port malfunctions, all of which could be resolved. Ten access ports were removed and replaced. This was necessitated by tubing leaks at or near the tubing connection to the port. In response to these events, the sponsor did make a design change to strengthen the area where the port tubing leaks had occurred.

There were an additional ten access port revisions which did not require port removal. In eight subjects the port was positioned so that it could not be accessed and two subjects experienced pain upon movement of the port. These events were resolved by repositioning and/or resuturing the port in place.

The LAP-BAND system is provided sterile. The system is sterilized using dry heat at the sponsor's manufacturing facility. Both bio-burden and biological indicators were used to validate the sterilization process. The results of testing indicated that, the dry heat sterilization process used for sterilizing the LAP-BAND system provided a sterility assurance level greater than 10 to the minus 6.

The sponsor has conducted shelf life testing to evaluate the performance of the device for one year expiration dating. This testing was conducted in real time and not as accelerated testing. All samples were exposed to a minimum of two full dry heat sterilization cycles and placed in normal storage conditions. Three phases of evaluation were conducted.

The sponsor looked at the physical testing of the heat seals, the functionality testing of the LAP-BAND assembly and sterility testing of the device. Results from all the testing demonstrated that after one year of storage under normal conditions, the packaging, functionality and sterility of the LAP-BAND was maintained. This is reflected in a one-year expiration date on the labeling.

The sponsor is continuing the testing and the device will be evaluated yearly, up to five years. The expiration date on the labeling can be modified as the

result from the additional testing are completed.

Both the physician and the patient labeling are still under review. Final physician and patient labeling will be completed pending recommendations from this panel and discussion with the sponsor.

This concludes my overview of the pre-clinical studies. Now, I would like to introduce Dr. Dan Schultz. He will be discussing the FDA's perspective on the clinical data.

PRESENTATION OF

DAN SCHULTZ, M. D., CAPTAIN, USPHS

DR. SCHULTZ: Good afternoon.

My name is Dan Schultz. You are not hallucinating that there is a Brian Harvey on the slide. Dr. Harvey, the internists who actually performed the clinical review of this product. Unfortunately for us, maybe fortunately for him, Dr. Harvey has since moved on to bigger and better things. He is now the Acting Deputy Director of the Division of Cardiovascular Devices and that has had an unavoidable conflict.

So, I am going to try to present his work as best I can. I feel somewhat like one of those pretty blondes who does the evening news and kind of reads things, but you could say I'm not a pretty blonde either.

[Laughter]

DR. SCHULTZ: Let's see. You've seen this several times but I think it bears repeating. The indication for this and any product is extremely important in terms of your evaluation and our evaluation as well. Basically what we are trying to do here is make sure that the indications that are proposed and ultimately adopted match the data that is provided.

So, as you have heard before, the LAP-BAND system is indicated for use in weight reduction for severely obese adult patients, with BMI greater than 40, BMI greater than 35 with one or more comorbid conditions, greater than 100 pounds over ideal weight, failed more conservative weight reduction productions and a commitment to life changes in diet and behavioral modifications.

Again, as you've heard--and I'm going to run through this quickly, because I think the reason we're here today is to listen to you rather than have you listen to me.

There was a prospective, multicenter trial performed in the United States. There were follow-ups conducted at three, six, nine, 12, 18, 24, 30 and 36 months. The inclusion criteria, as you've already heard, male or female patients between the ages of 18 and 55 and again, all of the criteria which were listed before.

Exclusion, pregnancy or intent to become pregnant. I guess that is not a 100 percent foolproof, as we have

seen, a history of drug or alcohol abuse, previous obesity surgeries, certain medical conditions which were previously and impaired mental status, which would make this operation inappropriate.

The primary effectiveness endpoint was the percent of excess weight loss obviated, as seen. The secondary effect in this endpoint's quality of life, change in BMI and overall weight loss.

The primary safety endpoint was the overall rate of adverse events. As you have heard--and this will be further discussed by Dr. Pennello who is going to present the statistical review--there were subset analyses done, looking at severe, serious, peri-operative, device-related and those requiring surgical intervention.

Again, as you have heard before, there was a total of 299 subjects at eight sites, 292 primary LAP-BAND subjects, seven secondary converted from the previous version of the device; 259 of those subjects or 89 percent were implanted laparoscopically and 11 percent were implanted via laparotomy.

In terms of the baseline characteristics, the average age was approximately 39, with a minimum of 19 up to 57. The average weight was about 293, a minimum of 193 to a maximum of 475; excess weight, 155, again, a minimum--and we thought it was important to present these intervals as well

as just the mean results. So, you can see the whole range of all of the baseline characteristics.

Next.

Again, more demographics, 15 percent males, 85 percent females, 81 percent caucasian, 15 percent African-American and four percent Hispanic.

Again, as has been previously mentioned, there were a significant number of patients who fall into this super-obese group. There was a retrospective analysis of comorbidities associated with the U.S. study. However, as has been alluded to previously, comorbidities were not tracked as part of the U.S. study, but were tracked as part of the international experience. Again, Dr. Pennello is going to go into some of these subset analyses and show you some of the differences that were obtained based on characteristics.

Again, this is pretty much a repeat of what you have heard. So, again, the data was sort of analyzed in many different ways, including the ITT analysis, the primary endpoint at 24 months and then all patients who had data anywhere between 24 and 36 months.

I think in terms of this, the most significant lines, at least, that I took away from this are the first line, the data at three weeks, showing approximately ten percent drop in excess body weight. Then after 12 months,

which sort of established the baseline and then the fact that from 12 months on, the results seemed to be reasonably consistent out to 36 months. Although as you have heard previously, the numbers do drop off fairly dramatically between 24 and 36 months in terms of the number of patients that were evaluable.

The same breakdown in terms of the absolute weights. There was a significant drop initially and a drop at 12 months, which sort of established the baseline and, again, fairly consistent results between 12 months and the 36 months at the end of the study. The same is true for BMI.

Again, as was mentioned previously, in addition to the primary endpoint, there were some quality of life measurements, including the RAND SF-36, the MBSR appearance evaluation and the Beck depression test. Dr. Pennello will be providing you with the data on each one of those.

Adverse events, again, as you have heard, they were broken down in various different ways, those greater than ten percent. Clearly, some of these were more significant than others. There were a number that were self-limited, but there were some that obviously were of a more serious and more directly related to the procedure itself, which did in fact require surgical intervention.

Next.

Looking at the issue of surgical intervention, this is clearly an area of concern for all of us. Surgical revisions were performed in 22 patients, device explantation in 48 patients or 16 percent and port revisions in 20 patients or 6.7 percent. As has been previously noted, the rate of adverse events did decrease significantly over the course of the clinical trial.

One of the things that we are going to be asking you to look at obviously--and this sort of directly relates--is the issue of appropriate training in order to perform this procedure.

As was mentioned earlier, there were two deaths associated with the study. One was a drug overdose and one was just reported recently and, I guess, as has been stated, the final diagnosis there has not yet been determined. That was on a patient who had explantation and subsequent gastric bypass.

You have also heard about the international retrospective study. Again, I think the significant point here is, they did measure weight loss. They measured adverse events as well, but the significant addition from that data was a measurement of changes in comorbid conditions related to obesity. Again, Dr. Pennello will provide you with those numbers and you have heard this before.

So, in summary, morbid obesity is clearly a major public health issue. There are obviously numerous treatment alternatives, both non-surgical and surgical, each of which has a different and somewhat unique risk-benefit profile. The LAP-BAND system has been studied under IDE in the U.S., approximately 300 patients, with supporting data from an international experience.

Overall, patients experienced a loss of approximately one-third of excess weight over one year, which appears to be sustained over the follow-up period of an additional one to two years. Approximately 90 percent of subjects experienced at least one adverse event, many of which were transient, but some were not. Approximately one-third of patients required an additional surgical intervention. About half of those were explanted and the other half were revised. This includes port revisions.

Finally, we believe that a reasonable assessment of risk-benefit can be derived from the data which has been presented in this PMA and we look forward to your discussion of that issue.

Thank you very much.

Dr. Gene Pennello will now discuss the statistical review and thank you.

PRESENTATION OF

GENE A PENNELLO, PH.D.

MATHEMATICAL STATISTICIAN, OSB

DR. PENNELLO: Good afternoon.

My name is Gene Pennello and I am a statistician at the FDA and I did the statistical review of the PMA and I will be presenting some of the results of this statistical analysis.

There were three clinical studies. As you know, there was an one-armed prospective U.S. study, a retrospective international study. As part of the literature review, there was a meta-analysis, comparing LAP-BAND to other procedures, the VBG procedure and the gastric bypass procedure.

Here is a table of some of the endpoints that were provided in the three studies. All of them included data on the percent excess weight loss, which was the primary endpoint in the U.S. study. Quality of life was evaluated in the U.S. study. Comorbidity was evaluated in the international study. They all provided safety results, adverse event analysis and the meta-analysis compared LAP-BAND to the two other procedures.

The primary endpoint of percent of excess weight loss--I'm focusing on two years of follow-up here in the U.S. study. I'm going to begin with the U.S. study.

There were three analyses and, as you have been told, there were 292 patients available in the efficacy

analysis group. At two years of follow-up there were weight measurements on 163 patients. The first line, I'm calling the complete case analysis, where you only considered those patients. There is the mean loss, the weight loss. The percentage of weight loss was 38 percent, with a 95 percent lower limit in the conference interval, 34.5 percent.

I should mention these results are slightly different from what has been presented because I did not use the completely revised data that came in as a PMA supplement because I couldn't do the comparisons I wanted to make with those numbers.

There was a second analysis, a 24 to 36-month analysis when the 24-month data were not available, but a 36-month weight measurement was available. That was used instead. There were 196 patients available there and the percentage of weight loss was 36.9 percent.

There was also an intent to treat analysis in which data were missing at 24 month. They interpolating between a 36-month outcome and the last previous observation available or if the 36-month outcome was not available, they just used the last observation and carried it forward.

The last two observations there show slightly less percentage as weight loss.

Thirty-eight percent excess weight loss translated to 17 percent of total body weight loss. It has been cited

in the literature that just a ten percent initial weight loss can reduce comorbidities.

There were some factors that seemed to affect the percent excess weight loss. The sponsor performed multivariate repeated measures analysis, using the generalized estimating equation model to correlate the outcomes within a patient, the repeated measures of weights. The biggest factor, according to this model, was the baseline weight where the lower your baseline weight, the higher the expected weight loss. The P value was .003.

For example, excess weight loss at one year was reported only--the mean was 31 percent for patients with a baseline BMI greater than 45 and 38 percent for a baseline BMI less than 45.

Other factors that seemed to influence the percent excess weight loss, the weight that was lost was greater for caucasians with a P value of 102. It was less for laparoscopy compared to the laparotomy procedure, although I have been told in the revised numbers, that P value changed from .06 to .15 or somewhere about. So, it is not as significant as I thought. There was difference from males and females.

I want to point out that this model adjusts for the effects--the effects of one variable are adjusted for all the other variables and I think that is important

because if you look at the raw numbers--for example, if you look at the males and females here, at one year, the males only lost 28 as a mean and the mean excess weight loss for females was 35.6 percent. That seems like there is a big difference there. The baseline weight is much larger for male than females. When you adjust out to a very large baseline effect, there is no difference.

There was significant variation by site in percent excess weight loss. The range in the mean was 25 to 53 percent. The range in the 95 percent lower limit of the confidence interval was 24 to 38 percent, except for one site where it was only 4.7 percent. That site had the highest Beck Depression Index, both at baseline and one year.

Also, the site with the highest lower limit, 38 percent, had the highest baseline weight, which would make you think at that site you would do worse overall in terms of percent excess weight loss. So, these kinds of findings suggest that there were differences in physician training and patient management.

The secondary endpoint in the U.S. study was quality of life. The measures of quality of life included these five components. There was data at one year and at three years. During a complete analysis, we just considered the data available at those time points. All the variables

were significantly improve and there were 165 patients on which data were available there at one year.

At three years, there are very few available data points, but even still, you got significant improvement in three out of those five variables.

On to the safety analysis of adverse events. That consisted of 299 patients, including seven who had the previous version of the device replaced. The mean length of follow-up was about two and a quarter years. The percentage of subjects having at least one adverse event was 88 percent. The percentage of subjects having at least a severe adverse event or an adverse event considered severe was 29 percent. For serious adverse events the rate was 40 percent. Device-related was 80 percent. I have listed here some of the more common adverse events broken down by those categories, including the port types of adverse events. The BS/PD is band slippage/pouch dilatation.

You could also compute adverse events per person-year. In the first year of follow-up, there were 264 years of exposure and there were 817 total events. So, that works out to three events per person, per year in the first year. If you assume a Poisson distribution on the counts, you get this as the upper limit, 3.3. You could break this down in terms of severe adverse events and device-related adverse events as well, an average of a third of an event per

person, per year, that was considered severe and about two device-related events per person year.

The adverse event rates were broken down by time, severity and surgical procedure. So, I have listed some of those results for you. Again, the total adverse event rate was 88 percent, but the percentage of patients having at least a peri-operative adverse was 43 percent, having at least postoperative even was 79 percent. Those two don't add up to 88, because you could have both a peri-operative and be counted both times there but only once in the total.

When you break this down by procedure, there was slightly more--the average event rate was slightly higher for the laparoscopic procedure and the laparotomy procedure, although the peri-operative adverse events, the right as slightly lower for the laparoscopic procedure. This is especially true for the severe adverse events. You get a larger difference there.

The rate of revision replacement surgery was seven percent and among those 22 subjects who had revision replacement surgery, the peri-operative adverse rate was 59 percent. That's larger than for initial surgeries, which might be expected because the conditions leading up to having revision replacement might lead you to have a more--to be at more risk of having an adverse event.

Also another possible explanation is, that there

were more open procedures during revision replacement surgery than initial surgery. This also was not significant because of the small sample size. So, it could be due to chance.

The rate of explantation was 16 percent; 48 subjects had their devices explanted. Among those, the band was replaced or another bariatrics surgery was performed in 40 percent of those patients. In 60 percent of those patients, the band was removed and the anatomy was essentially left intact.

On to the international study. This was a retrospective study, which they collected available patient chart information. As you already know, the subjects were enrolled only after 50 LAP-BAND procedures were performed by the surgeons. So, we are looking at very experienced surgeons here. These are the six sites; 441 subjects in total were enrolled.

The percentage has weight loss at two years of follow-up, the mean was 50 percent. There were 272 out of the 441 on which you had weight measurements at two years follow-up. This 50 percent is larger than in the mean--in the U.S. study at two years of follow-up. That was only 38 percent.

A possible explanation is, that in the international study, the patients on average weighed a bit

less than in the U.S. We already know from the U.S. study that baseline weight--the larger your baseline weight, the less you're expected to lose in terms of percentage of weight loss. So, that is a good explanation for it.

The international study had data available on comorbidities and here I've listed some of the comorbidities--well, I'm listed at two years here, with a significant--the comorbidities at which you found significant reductions from baseline.

For example, for shortness of breath, the rate was 60 percent and that got reduced to 45 percent. That P value was very significant. All of these are significant.

There were two analyses performed. The first analysis was last observation carried forward analysis, in which if the data weren't available, you used the last observation. The sample size is 320 there. I asked the sponsor to also do a complete case analysis to see if there were any changes. All the inferences were the same here. The same variables came out significant, except for depression which went from not being significant to now being significant in this complete case analysis.

Adverse events in the international study, the rate was only 38 percent, compared to 88 percent in the U.S. study. There are probably two explanations for that. This was a retrospective study, in which you are only looking at

patient charts which may have tended to report the more serious adverse events. So, what I have done here is also listed an addition column of serious adverse events, the rate of serious adverse in the U.S. study to compare to the international study. You will see that they are a lot more similar.

The second reason for the rates being lower could be that the surgeons were a lot more experienced in the international study.

I thought this was interesting. One of the rates that was higher in the international study than the U.S. study was port leak, although this is not significant, five versus two.

Both the international study and the U.S. study had about two and a quarter years. The mean years of follow-up was about two and a quarter years. I just stated those.

On to the meta-analysis which compared the LAP-BAND to gastric bypass and vertical-banded gastroplasty. I am labeling them L, G and V in the next few slides. There were over a thousand articles abstracted, but very few made the criteria to be included in the study. For percentage of excess weight loss, only 49 articles were used in the adverse event analysis and 95 articles were used.

These were some of the criteria data on percent

excess weight loss or adverse events. The authors had to be the investigators. The procedure was the focus of the article. The studies were mainly uncontrolled and did not usually address loss to follow-up.

The sponsors used generalized estimating conclusion models to predict and excess weight loss for the three procedures. They did not have individual weight losses on the patients. What they used were just the summary numbers in the articles when they developed this model. The percentage says weight loss at two, three and four years of follow-up are given in this table.

From LAP-BAND, it went from 61 percent to 63 percent. For VBG it was 60 and reduced down to 51 percent for a gastric bypass, 73 down to 63 percent. These numbers are all much larger than in the other two studies and explanation is probably publication bias which might inflate the numbers here, although I think what we're trying to do here is trying to compare these procedures and not necessarily focus on the absolute numbers.

The baseline weights were less for LAP-BAND than the other procedures in the article. The sponsor did include baseline weight and adjusted for it in the model and it didn't make any difference, however.

On to the adverse events in the meta-analysis. These are peri-operative complications. I have just listed

a few here, the first five. In general, the LAP-BAND had a much lower rate of adverse events, specific adverse events than the other two procedures. Some of these are because there are just price-specific adverse events here.

These last two I'm just showing because these were gastric perforation and port infection were way higher in between the other two procedures for LAP-BAND.

Postoperative complications, the sponsor did two analyses. The initial analysis was based on all articles and, again, in general, the LAP-BAND seemed to have lower adverse event rates than the other two procedures. Those are listed a the top. At the bottom, there were a few, however, in which the LAP-BAND rate was either above or in between the others.

There was a second analysis that was done because it was hard to get a handle on the mean years of follow-up for each of the--for the articles. For LAP-BAND, the maximum length of follow-up was no more than five years in any of the articles. For the other two procedures, the maximum length of follow-up could be as high as 10 or 15 years. So, to try and make the mean length more comparable, an analysis was done and was restricted to a maximum length of follow-up to five years.

That's the next slide.

So, this was restricting the articles to a maximum

follow-up of five years. In general, the conclusions were the same.

For mortality, peri-operative mortality, the LAP-BAND rate was .09 percent compared to about a half a percent for a vertical-banded gastroplasty and .33 percent for gastric bypass. For all causes of mortality if you restrict only to five years of follow-up, you also get a lower rate for LAP-BAND.

For reoperations, the LAP-BAND reoperation rate was about that of the vertical-banded gastroplasty. Gastric bypass was about half of the other two procedures.

I'll conclude with some comments on the validity of the statistical analyses. There was missing data in all of these analyses at two years of follow-up for percent of excess weight loss. When you do the complete case analysis, what you are assuming is that the patients who are missing can be modeled the same way as the patients who are not missing. That is an untested assumption.

However, the sponsor did do several analyses to try to see if there were any different conclusions would come about from those. The last observation carried forward intent to treat and they all seemed to come up with pretty much the same conclusions.

The GEE model for repeated measures, I just want to point out that, that was their way of correlating the

measurements across time within a patient. I wanted to point out that, if you get the correlation structure wrong, the estimates are valid in these GEE models. So, it's a nice way to do the analysis.

The U.S. study was a one-armed study. It did not have a comparator device, which in the ideal world, you would like to have a comparator in your study. The international study is retrospective. It did not follow the patients over time.

For example, one problem with this is--that could be a problem is that, the patient charts that were available may not be representative of the target population.

The meta-analysis, well, it's always difficult to do a meta-analysis. There is probably publication bias which inflated the excess weight loss numbers and reduced the adverse event rates. The comparisons that were made are confounded by study effects and varying lengths of follow-up. There were some dramatic differences in the adverse event rates that I think are probably hard to ignore.

Now, Kathy will come up and talk about the post-approval study.

MS. OLVEY: Thank you, Mr. Chairman.

I'm going to prevent an overview of the sponsor's proposed approval study for the LAP-BAND system. The proposal includes four separate studies. Each of these

studies have already enrolled subjects and continuation of follow-up, according to each study's protocol will occur post-approval.

Two studies are being conducted here in the United States and the other two at several international sites.

The two studies to be continued in the U.S., both were done under IDE. The first study includes the 299 subjects discussed in the PMA. Enrollment in this study is complete. The protocol called for three years of follow-up, however, at the time the PMA was submitted only about 89 subjects had follow-up for three years. The sponsor is proposing to continue following all subjects post-approval, until three years of follow-up is completed.

The second U.S. study was also approved under the same IDE. After enrollment of the initial 299 subjects was complete, the sponsor requested for an expected access arm. Approval was given for an additional 240 subjects. When last reported, about 64 subjects had been enrolled in this second study.

In this study, there are some investigational sites that participated in the first study and then several new sites. The other two studies are being conducted at sites outside the United States. Both of these studies were initiated in 1998. One study is a prospective study of 225 subjects. Follow-up on all subjects will continue for five

years.

A retrospective study is also being conducted and those 441 subjects have been enrolled. These subjects will also have five years of follow-up.

The protocols for the four studies are similar. All four measure weight loss and the number of adverse events. Changes in comorbid conditions are evaluated in three studies, although not for the first U.S. study. In the second U.S. study and the percent excess weight loss will be compared between new and experienced sites.

Another difference is the length of follow-up, one or three years for the U.S. studies, but five years for both international studies.

FDA has concerns related to the length of follow-up for the U.S. portion of the proposed approval study. This is addressed as one of the discussion points. We would like the panel to address the appropriate length of follow-up for pre and post-approval studies.

Thank you.

DR. KALLOO: Thank you, FDA.

The panel discussion portion of the meeting is now open and while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the panel.

The first speaker is Dr. Mark Talamini, who is a

primary panel reviewer and lead discussant.

PRESENTATION OF

MARK TALAMINI, M. D.,

PRIMARY PANEL REVIEWER AND LEAD DISCUSSANT

DR. TALAMINI: Thank you, Mr. Chairman.

I just have a few slides. I'm a general surgeon in an academic practice. About half of my practice is laparoscopic and the other half is open, usually complex gastrointestinal surgery. I just want to spend a few minutes trying to frame some of the issues that we need to discuss today, from the point of view of the world of general surgery.

First, regarding laparoscopic surgery, there's no question that it is the surgery of the future. There have been a number of issues it has brought up in the ten years that it has become immensely popular in general surgery. One of them is whether lowering the threshold for an operation is an okay thing or not.

There is no question that in most laparoscopic operations, the threshold for surgery has been lowered. I can think of two very clear examples of this. One is laparoscopic cholecystectomy and the second is laparoscopic donor nephrectomy. Now, in both of these cases, we clearly have an increase in the number of patients showing up for the operations, in the case of donor nephrectomy, to give

their kidneys, in the case of cholecystectomy, to resolve a symptom.

In the case of cholecystectomy, there was a price tag for that. There is an increase that's fairly clear in the risk of bile duct injury and we have paid a price for that as a whole population. However, on balance, the risk-benefit analysis seems to be that, that still is a good thing.

Donor nephrectomy might be a little bit more similar to what we are talking about today. That's an example where that has provided a lot more organs for transplantation because patients were simply more willing to undergo the laparoscopic operations, as many patients with morbid obesity may be willing to undergo this operation.

Second, should the laparoscopic operation be just as good as its open counterpart? Initially, we said the answer to this question was unequivocally yes. I think for most procedures, it still should be yes. For a laparoscopic anti-reflux operation, I tell my patients if I don't think it's going to be as good as the open operation, I'm going to stop and make an incision and make sure it is as good as the open operation.

Now, in practical terms, that is not always true. For the large part, I think it is true. Today, we're talking about a situation where the data suggests that we

know from the outset that the laparoscopic operation may not create as much weight loss as some of the open operations that we have been talking about. I think that is something we need to address.

Next slide, please.

Now, I put these up here mostly to frame the possible skepticism of the surgical community regarding devices living where this device lives. In terms of reflux operations, we have the experience of the Angelchek prosthesis. I don't even know if I've spelled it right, but I know we don't use it anymore.

We now have two new things on the horizon that are being used now that we are going to wait and see, I think, within the Streppa procedure and the endoscopic sewing machine. The reason these things are important is, these are devices that set at the GE junction and the GE junction moves every time you swallow. I think it is significant that we're talking today about a device that lives very close to that GE junction that moves every time you swallow.

Similarly, in the world of obesity surgery--and I am not an obesity surgeon--but again, surgical history has examples of operations that are now long by the wayside. I think that we have to factor that in. It certainly has nothing to do with this application today, but it does speak to a possible atmosphere of skepticism that surgeons and

other physicians may carry into this discussion today.

Now, another important issue that has occurred in laparoscopic surgery that I think is important to understand is what I've called subspecialty drift. We have examples where procedures that use to be well-contained within a group of surgeons who knew those patients well and knew the issues well, suddenly were taken over by, quote, laparoscopic surgeons. This has occurred with cholecystectomy. It has occurred with anti-reflux surgery where you have a set of thoracic and GI surgeons who did all the reflux surgery. Suddenly a huge influx of laparoscopic surgeons and that is one of the potentials here as well.

Again, it doesn't speak directly to the application. I would be unfair if I said that it did, but we can expect that, if once approved, there will be a lot of laparoscopic surgeons entering this arena. This is a particular arena where expertise regarding the non-surgical management of these patients is incredibly important. So, I think those are issues we have to keep in mind.

Finally, I put this up here as something that I have learned as a panel participate. That is what FDA approval really means to different groups of populations. Again, it doesn't speak anything to the approval of this application today, but I just got back from DDW three or four weeks ago and immediately heard somebody on the radio

using FDA approval in their marketing of a new technique.

Now, that isn't necessarily wrong, but it has emphasized to me the importance of labeling, training and indications for what we do here.

So, I just have those few comments to sort of frame our discussion as a panel as we talk about the questions before us today.

DR. KALLOO: Thank you, Dr. Talamini.

We will now address panel discussion points and establish a consensus for each issue.

The results of the U.S. study demonstrate a 38 percent excess weight loss at 24 months. Please discuss or comment on the clinical significance of these results. I would like to start off on my extreme right, Dr. Sawicki and ask for your comments and we will go around the table, at which time Dr. Talamini will summarize the panel comments.

DR. SAWICKI: Can you be a little bit more specific in your question? It seems rather vague or may it is intended to be vague.

DR. KALLOO: Yes, what do you think about those results specifically in terms of the 38 percent excess loss?

DR. SAWICKI: Do you mean whether or not it is significant or sufficient?

DR. KALLOO: Yes.

DR. SAWICKI: I think it is both significant and

insufficient, insofar as what we're trying to achieve here is to reduce the patient's weight sufficiently so that you can reduce their comorbidities. You're not trying to body shape them or have them to lose enough weight that they look better, but really that you achieve control of their comorbidities. I think that weight loss probably is sufficient to achieve that.

DR. KALLOO: Next, Ms. Newman.

MS. NEWMAN: You know, because I saw other numbers in there and my impression from this data was, it wasn't that significant from baseline. Maybe as far as the total weight, but I think that has to be brought out to the patient what they can expect as far as weight loss.

DR. KALLOO: Dr. Gabril.

DR. GABRIL: I think this is clinically significant. This translates to 17 percent of baseline weight loss from we are told. The literature has shown that ten percent reduction will improve comorbidity. So, I think the 38 percent is acceptable.

DR. STEINBACH: Thirty-eight percent is acceptable weight loss. Twenty-four months is short compared to other studies. So, we have to assume that the weight loss will be constant thereafter.

DR. KOZAREK: I think it is a significant weight loss. Fifty out of 150 pounds, it certainly perhaps not as

good as some of the open surgeries with gastric bypass. Given decreased morbidity, it might be an acceptable trade off.

DR. CHOBAN: I think it is real weight loss. I don't debate that. I guess I have a couple of concerns with it in that, I've spent my last nine years with a large practice in obesity, with a definition of surgical success being 50 percent of excess weight loss at five years.

I think one of the other operations that didn't get mentioned on the notorious history of obesity surgery is Pace gastroplasty. So, I'm really concerned about a modest, a 40 percent albeit real weight loss at only 24 months because the natural history of the disease has been slow weight gain with periods of long term follow-up.

So, is that going to continue to hold up?

I think when we look at the comorbidity events and improvements, they are substantially less than has been seen with gastric bypasses as even the most common example and even with some more malabsorptive operations, although you're trading for other problems.

I think the issue of laparoscopic versus open is becoming more and more of a moot point, as any of the operations can now be accomplished laparoscopically, although albeit it with steep learning curves and requiring significant surgical technical expertise.

So, I guess in terms of--I think the weight loss, the follow-up duration has me very concerned. Can we ask for clarifications in this.

DR. KALLOO: Yes, you can ask for clarifications.

DR. CHOBAN: In terms of what the initial study protocol looked at, the clinical trial would be completed after 36 months of follow-up. Sort of why change it now for 38 percent. I would take that interpretation as they felt that that was result was compelling enough to come earlier. If the initial efficacy outcome was going to be 50 percent, do you just change it when you don't get what you're hoping for?

DR. O'BRIEN: Is there a particular person who wold like--

DR. CHOBAN: I'm not sure who would be the best to address that, maybe Dr. MacDonald or Mr. O'Brien.

DR. O'BRIEN: Well, you commented on the changing weight pattern over time. Could you clarify the points you would like me to make? I can comment on the natural history of weight loss after this procedure, which might help you.

DR. CHOBAN: In Dr. Mason's paper that was cited as--why to change it to 25 percent of excess weight. It was also talking about at a ten-year follow-up point.

DR. O'BRIEN: Sure, I understand.

DR. CHOBAN: So, if you are only at 38 percent at

two years, where are you going to be in ten years.

DR. O'BRIEN: Yes.

DR. CHOBAN: Would you expect it to follow the line of VBG. I think you're going to have trouble being there 25--

DR. O'BRIEN: We don't know at ten years. I know from my patients getting out to six years. The pattern of weight loss after the LAP-BAND has been different than we saw with the gastric bypass, which tended to peak at one year or two years and then would flatten or taper. Certainly, after gastroplasty or VGB, that would be more of a pattern.

There is a steadier rise over the first two years. Then in my experience, it just crept up gently beyond that, because we still have control. We have control of the level of gastric restriction. Whereas, after the other procedures, we had no control after the day of operation.

So, I anticipate that we will have at least a stable weight and possibly an increasing excess weight loss over time. My own experience fits in with that.

DR. CHOBAN: Okay, thank you.

DR. KALLOO: Dr. Talamini?

DR. TALAMINI: It is clear to me that the weight loss is not as significant as the other operations and perhaps not as significant as might have initially been

expected with this advice.

I think that I agree that the follow-up duration is short and it sure would be nice to have three years on all the patients, to make things a little bit clearer.

DR. NELSON: Well, the only new point that I raise is that, simply on the basis of efficacy--and not being a surgeon--it seems to be that it is clear that it is somewhat less effective although it does achieve what appears to be a minimal amount to reduce comorbidities.

The larger question of whether gastric obesity surgery will reduce comorbidities is an important one and it really isn't addressed any of the studies. There is a suggestion from the international study with a tremendous fall off or drop out rate that, that amount may be a very small amount. In general there are immediate postoperative complications from any surgery and we are weighing them against an unknown benefit of comorbidities.

If this were just a new procedure, I guess it wouldn't necessarily proven for weighing against other accepted gastric surgeries that are already in existence. They haven't shown necessarily the same decrease in comorbidities either.

So, the first one is hard to answer in complete isolation without complications, but it seems to me to be the minimum criteria for weight loss that would be

effective.

DR. FOOTE: The comment that I have to add is not necessarily about comorbidities, but about patient's expectations. I think the slide that was presented initially with Dr. Talamini's presentation is apropos. One of the things that I have become aware of at the meeting today is the social implications of obesity, in addition to the medical implications.

I think that regardless of what status that device is given today, I think it is important in the patient labeling that, patients are made very clear about what their expectations are from this device, so that they don't necessarily think they're going to go from a size 20 to a size 8 in a year and a half, as may be expected in a more exceptional individual and that they have more realistic expectations to be given, as an example, given in examples, for example, what type of weight loss to expect.

DR. HIRSCH: I don't have too much add though, except to say that, first of all, the production in comorbidity is not a linear function of weight loss. It's a strange thing but sometimes a little bit of weight loss can produce a great change in comorbidity. That seems particularly to be true with Type II diabetes.

It looks like this procedure, at least, out at the two-year level is somewhere between the best of drug and

diet, et cetera, which can affect about a ten percent loss of body weight under the most ideal of circumstances and then something like gastric bypass, which is much better than that.

So, this is sort of somewhere in the middle of that.

What concerns me is, that it is at the two-year level and the extraordinary history of obesity is, under the best of influences and greatest of ideas and so on, with the passage of time treatment seems to somehow vanish and not do well. So, I am concerned about what is going to happen with these people years after the surgery.

I note that something like 40,000 devices have been sold. It would be interesting to know whether the rate of sale keeps up and is multiplying. This would be a sort of rough measure of how good this all is.

DR. BARANSKI: I too don't have too much more to add. I think they originally set out a goal of about 50 percent and ended up with 38, which seems reasonable and far above the state it has been ten percent reducing comorbidity. It would have been nice to have a few more--to involve the study in the reduction of the comorbidities. I think you have to submit that they are clinically significant.

DR. LINNER: My feeling is that, 38 percent or

38.7 percent at two years is not adequate, certainly not adequate for patient expectation. It has been shown that the comorbidities improve and I think that's true. I don't think a two-year study is an adequate time to follow something like this particular addition to our surgical armamentarium.

The restrictive operations are all afflicted with a problem sort of like Catch-22. If you want to get more weight loss, you tighten it up. If you tighten it up, you have more problems. Now, I think this has been presented extremely well and I commend the sponsor for the thorough search, but I do think this study has got to go on for a longer period.

DR. KALLOO: Dr. Talamini, would you summarize the panel comments?

DR. TALAMINI: Mr. Chairman, I think that the panel is saying that the weight loss and in answer to question one, the weight loss demonstrated is significant and appears to be associated with reduction in comorbidity but is clearly less effective than the other surgical therapies.

The committee, I believe, is expressing reservation about looking at the two-year data as opposed to the full three-year data originally proposed for the study.

DR. KALLOO: Okay, question number two.

Please discuss the indication for use as proposed for the LAP-BAND system. Based upon the data provided in the PMA, please identify whether there are subpopulations that should not be treated by implantation of the device.

DR. SAWICKI: First, I have a couple of questions for the sponsors. In terms of subpopulations--and I'm not sure if these are relevant or not. At the time of placement of the LAP-BAND, did you allow your surgeons to simultaneous perform cholecystectomy?

DR. O'BRIEN: Yes.

DR. SAWICKI: Did you see a higher infection rate in those patients?

DR. MUNJAL: The investigators did perform concurrently while the LAP-BAND was being placed some cholecystectomy and the infection rate was not increased.

DR. SAWICKI: Do you have an idea of roughly how many were performed simultaneously.

DR. MUNJAL: I can get you--I don't have it here handy, currently available.

DR. SAWICKI: Okay.

If during the course of the procedure, the surgeon injured the intestine, was the procedure aborted or continued?

DR. MacDONALD: I'm not the sponsor, but I'll give it a shot.

I'm Ken MacDonald, again, at East Carolina University.

That was up to the individual surgeon. That is why there was some variation. In two cases where the stomach was entered during the dissection and the band, after the stomach was repaired, the band was then placed. Two of those resulted in band erosion. Because of differences in opinion and stuff, some of us would not have placed the band at that point.

So, I know of no cases, but I can't say for sure until somebody reviews it. I know of no cases where the small intestine or colon was injured and then the band closed.

DR. SAWICKI: Okay.

My last question is, patients with cirrhosis, were they included in the study or excluded? So, if they started the laparoscopy and found a macronodular cirrhosis, could that investigator continue to place the LAP-BAND if he thought it was safe to do so or is that patient excluded?

DR. MacDONALD: Again, I have no knowledge of that particular event occurring, but were that to happen to me, I would back out very quickly and not perform the band. I only know of one isolated case where anybody went on with a bariatric procedure when that happened. So, in most cases, yes, I think most surgeons would abandon any sort of

bariatric procedure.

DR. SAWICKI: Okay, thanks.

So, the areas I would consider for populations that would not be treated would be patients who I think there is a significant bowel injury during the course of the operation because of the risk of infection of the device. Patients who are undergoing chronic, long term steroid treatment, it is not clear to me that the safety of that is clear.

I would like to see the data on cholecystectomy and any other simultaneous procedures that might have been performed during the course of the study.

DR. TALAMINI: So, primarily you are talking about things that would increase the incidence of infection with the implantable device?

DR. SAWICKI: Also, cirrhotics, patients who would be at higher risk from bleeding, et cetera, during the course of the operation. I don't see based on the data presented in the PMA other subpopulations that could be identified preoperatively who I would exclude.

MS. NEWMAN: We brought this up before, because there are differences between the international and the U.S., we are assuming it was surgeon. I think there could be differences within the populations. I don't really think it's been analyzed enough. So, it is hard to say if there

are subjects--is it based on weight? Is it based on age?

I don't know. I think I would have liked to have seen more of an analysis of the individuals, maybe possibly what was their preoperative and whatever to see if there are some differences. There is a subpopulation that may not do as well.

DR. KALLOO: Dr. Gabril.

DR. GABRIL: I think I would include all patients who have portal hypertension, complications that led to portal hypertension. The groups that are excluded here are esophageal or gastric variances, but there are patients with portal gastropathy or ascites, for example. So, I think in general, any patient who has portal hypertension, regardless of which complication they have, should be excluded from this.

The second one, I think, is the chronic pancreatitis, where there is a possibility of splenic ventral (?) that could lead to gastric varices down the road. So these patients should be also identified.

The question with Barrett's esophagus, these patients have a very common gastro-esophageal reflux, and I think they should be careful with this group of patients at least.

The final one would be the dismotility disorder, esophageal or gastric. I think these patients again--GE

reflux is common and a subgroup of patients have esophageal dilatations and it is a problem with regurgitation, especially in the morning and so on. I think this group of patients should be also evaluated preoperatively for motility disorder and should be excluded.

DR. STEINBACH: The subpopulation that should be excluded are the ones who are unwilling to restrict their diet. This is just a device to help people to do this. Since the protocol started, there are a fair number of patients who are sweet eaters or whatever. They are the ones who have failed. If we now went back over their back inventories, could we identify this group or would this be part of the patient labeling, to warn them that you still have to restrict your diet? This does not replace it; it supplements it and maybe more emphasis in patient selection.

DR. KOZAREK: Can I ask the sponsors whether we have any idea about H2 blockade or PPIs taken before and after the device or after the procedure has been performed?

DR. MacDONALD: I'm sorry, what is your specific question?

DR. KOZAREK: Well, quantitating the degree of reflux patient, you are putting a relative barrier to the distal stomach by making a small pouch. If you get somewhere, 50 percent of your patients on proton pump inhibitors or H2 blockers before, what is the incidence of

reflux afterwards? That would help me to decide whether a florid anti-reflux or--other than severe esophagitis, which are one of the exclusion criteria should be included in this patient group.

DR. MacDONALD: As you saw in the presentation, it was a significant--gastric esophageal reflux symptoms were significant, one of the highest percentage. While most of that was mild or moderate, it was still present. H2 blockers or proton pump blockers were used empirically and transiently in most of those cases.

DR. KOZAREK: Can you quantify that, whether it was ten percent before and 80 percent afterwards or 80 percent before and ten percent afterwards?

DR. MacDONALD: Okay, can you all work on that for me?

Reflux, preoperative reflux symptoms, I think, are a warning signs for problems. A large hiatal hernia would be a warning sign for problems. In my personal biases, those are cases that I would need to evaluate very carefully and, perhaps, even exclude for this. So, you are correct to be focusing on this because it is a--that's my personal bias. If somebody has bad reflux preoperatively, I'm probably going to suggest alternatives.

DR. KALLOO: Why don't we go ahead while the data--

DR. MacDONALD: May I answer just one previous question? We have the data. Cholecystectomies were performed in 33 patients, so 33 of the 299.

DR. KALLOO: Okay, we will come back to the data. Let's move along.

DR. O'BRIEN: If I can just make a comment on the point that you have raised, because we published a paper on that topic.

DR. KALLOO: Do you specifically want a response from him? Is this a previous point?

Okay, yes, please; then go ahead.

DR. O'BRIEN: We didn't expect so, but we found it to actually be an indication for the procedure. It's been very effective in stopping reflux. We have studied these patients carefully and for the moderate and severe reflux patients, there is cessation of disease. We had 16 out of 18 patients had no residual disease, who were on proton pump inhibitors.

DR. KALLOO: Okay.

DR. CHOBAN: In looking at the distribution of the data and in coming back a little bit to the efficacy, looking at the population of Type II diabetics if, in fact, the weight loss is in that subgroup even less efficacious and you're impacting less favorable on the resolution of their disease that, that might be a population that gets

aimed to another therapy perhaps.

I guess the other concern with the super obese, again, in coming back a little bit to how much is enough and if you have something that is not as effective, how do you direct it? I think within the United States, at least, one of the concerns is funding mechanisms for patients. If you are confronted with insurance policies that have single lifetime benefits of therapies that perhaps--and it may not be a contraindication, but a patient labeling issue to make sure patients are advised that, if you only get one ticket, you'd better decide how you use it.

So, the diabetics and super obese tend to not do as well. That might be a group that needs special advice.

DR. TALAMINI: Well, I think that the panel has already discussed in good detail both sides of the equation here, the issues that could potentially reduce the comorbidities and problem and trying to identify who would most benefit or less benefit. I asked that question this morning, whether the data gave any hints to that and the answer to me was, no, it does not.

What I do find both interesting and troubling is that, for the severe refluxers, this looks like it is an Angelchek prosthesis. For a bunch of the others, we have created an obstruction. So, I think at least a percentage of those who are listed as problem, the problem being listed

as reflux, what we have really done is created an obstruction and they are interpreting that as reflux.

I especially make that comment after hearing the professor say that, his severe refluxers were improved because this was acting like an Angelchek prosthesis in my mind. So, I think it sure would be nice if in all of these patients we had a barium swallow or a sini(?) to really know what is going on at that GE junction. I understand we don't and won't have that data.

DR. NELSON: No new comments to be added.

DR. FOOTE: I have a--and this may be a rhetorical question. I'm not sure if there is anyone from the company or any of the investigators can answer.

Was there any standardization of the postoperative behavioral management for these patients? Like the other investigators, I got a copy of a booklet that was given. There was a mention made earlier of one of the individuals who had had the treatment that there was a very intensive group therapy along with the dietary management.

I wonder, as an individual kind of looking from the outside, not being involved with these patients on a day to day basis, if one of the differences that may explain patients that did very well from those patients who didn't do very well at all, may be explained by a difference in the postoperative management that these patients got.

If there is someone from the company or one of the investigators who would like to comment on it, I would like to know the answer. I'm also wondering a lot if no one has really looked at that kind of data.

DR. MacDONALD: There was no more standardization in behavioral management and general counseling than there would be for any other group of bariatric practices. The sites were chosen on the basis that these individuals were already experienced in bariatric surgery, and they sort of had these baseline requirements set for counseling. They saw the same tapes. They read the same material and signed the same seven-page consent form, which, you know, went through a lot of that discussion. But exactly how it was discussed and the type of stuff was really not standardized much at all any more than normal. That's a difficult thing to try to standardize.

DR. FOOTE: Based upon your experience as a bariatric surgeon dealing with a variety of procedures, including this one, what recommendations would you have, you know, to try to standardize the type of benefit that patients may get, appreciating that behavioral modification after surgery is so important?

DR. MacDONALD: The best thing you could do is with the surgeon training, the training programs that they have proposed to you, and I think they would plan to spend a

lot more time on that sort of thing with the knowledge that has been attained in the last five years during this study.

Again, this is a new operation with laparoscopy itself being relatively new, starting five years ago, and we know so much more, I think, collectively than we did at that time. So with the collective experience we have, that would be a strong part of the training of the surgeons.

DR. KALLOO: Okay. Thank you.

DR. HIRSCH: I really don't have much. It's an odd situation because, obviously, if anyone ate less without this thing, they would lose exactly the same amount. I mean, no one supposes anything magical is happening here. So the issue is that somehow putting this thing in in some way increases the motivation to eat less by virtue of adverse effects or whatever, or benefit of more satiety, which is an unlikely thing, I would think, and it's sort of a sliding scale. If you do even more with the bypass, it's even worse when you eat more. So it's just sort of putting it--it sort of starts way at the other end, like from jaw wiring, which was done years ago, in England particularly, for the treatment of this. And this is a sort of internal version thereof.

No one thinks this has anything to do with the cause of obesity because, clearly, you don't get obese because you don't have a silicon band. You know, you

understand this is not a treatment in the usual sense. It's inducing an aversive state. And the whole psychology of how people respond to aversive states and what they mean to people is a very subtle matter. I think we have no way of answering that at the present time.

DR. BARANSKI: One of the concerns that I have--and I think that Dr. Talamini alluded to that--is that population may develop that doesn't fit the criteria instead of having an excess weight of over 35 percent and so forth, that those numbers continue to be dropped. And I think with this supposedly more simple procedure and the simplicity of the procedure, it seems that people are always looking for an easier way to lose weight, and that this procedure may be offered to some individuals that really shouldn't and don't qualify for it.

DR. LINNER: As I understood the question, it was contraindications to the surgery. Was that the basic question?

DR. KALLOO: Indications and selection of subpopulation that should not--

DR. LINNER: I think contraindications as were listed by the sponsor were about the same as we use, inflammatory bowel disease and that sort of thing.

With respect to patient selection, I found that in restrictive operations, the patient will need more

instruction and they need to be more cooperative. We had patients who failed and this is an operation that's no longer being done, but the horizontal gastroplasty is a restrictive operation. And those patients, when they did fail, many of them would say, well--or we'd ask them, are you eating sweets, are you drinking--or eating ice cream and so forth? And some of them would say, well, that's the only thing we can eat.

I think you have to approach the patient, if this sort of device is applied, super-obese people I don't think generally are good candidates. It's very difficult to bring a super-obese patient down to significant weight loss without something more than pure restriction. So I think that's one contra--not necessarily a contraindication, but the super-obese patient has to know that this operation isn't going to work for them unless they apply an awful lot of effort. And they would be better served with something like a gastric bypass.

But I think patient selection in this type of surgery is extremely important.

DR. KALLOO: Okay. Dr. Talamini, will you summarize the panel's comments?

DR. TALAMINI: Mr. Chairman, with respect to subpopulations that should not be treated by implantation, the panel has identified a few categories of patients, those

perhaps at increased risk of infection during the procedure, those with portal hypertension and, therefore, gastric or esophageal varices, those with dismotility disorders, and those with large hiatal hernias.

With respect to the indications already established by the company, the panel largely agrees with those indications, but I think would benefit from understanding more about which subpopulations will do well with the operation and which not.

DR. KALLOO: Okay. Question 3. Eighty-eight percent of patients enrolled experienced at least one adverse event; 33 percent of the events were rated as severe. Please discuss the impact of the number and severity of adverse events on patients implanted with the LAP-BAND system.

DR. SAWICKI: Well, this is really at the heart of what we're after here, and it's probably the most difficult question to address.

Part of the high numbers of adverse events is probably due to the learning curve, as I think the international studies have suggested. The other part is inherent to the system, and that's been emphasized here this morning with the problems related to, quote, band slippage or pouch dilatation and, I think, a relatively high number or percentage of reoperations. And that to me is the most

concerning aspect of this device and procedure, that out of 292 patients, there were 70 reoperations for one reason or another, either to remove the device, revise it, move the port, whatever. And that's very concerning to me.

On the other hand, when you look at the other surgical alternatives, it's on par with VBG problems. So I think the device that is comparable in its effect to the VBG has a similar reoperative rate and complication--or, actually, in many categories, a lower complication rate. So I think to a certain extent that's acceptable.

DR. KALLOO: Ms. Newman?

MS. NEWMAN: I think and compare it to other--like you said, it's true, but I think that when we go out there and say non-invasive, laparoscopic patients come away thinking, wow, you know, in and out, no problem. And I read on your mild--you didn't have it on your slide--that the mild adverse events were really mild, but they could still be taking medications, which goes back to you, what medications are they taking. They could be taking antacids, H2, everything, and you don't seem to have that. I guess that wasn't important to you that they have mild but they're still taking medications for their "mild" symptoms.

So I am going to jump on the labeling, which we'll get to later, because you're very light on that. You've got to tell these people these issues, the fact that they may

need medications for these mild symptoms, and I'd like to know what the data is. How many did take medications? What medications did they take for the mild symptoms up to the ladder to the severe? Because I think that's of interest.

DR. KALLOO: Dr. Gabril?

DR. GABRIL: I have a question if the sponsors can answer. The GE reflux, the frequency was about 33 percent. Did any of these patients undergo endoscopic evaluation, upper endoscopy?

DR. KALLOO: I think there are probably two questions we could try to get you to answer: medication treatment and endoscopic intervention for evaluation. How common or frequently? And if you need time, we can--apparently not.

DR. MacDONALD: The question was did any of these people get endoscopic evaluation, and I'm going to have them look for the data. In my personal series, we endoscoped only one person and found no specific abnormalities. Most patients were evaluated by barium swallow, which was the best way to--it's much easier to diagnose the slippage or some kind of obstruction problem in this particular case with the barium swallow than endoscopy.

DR. GABRIL: How did you establish the frequency of the GE reflux? Based on the symptoms?

DR. MacDONALD: Just based on symptoms. It might

have been heartburn, so an investigator would record that. Probably it was just pyrosis or heartburn that was the primary symptom recorded.

DR. GABRIL: The problem is the majority of patients with esophagitis are asymptomatic. And now we might miss a very important part of complication probably from this procedure, having esophagitis and not knowing that, you know, as part of the adverse events in this study.

DR. MacDONALD: Of course, we don't even know what the baseline for the normal population is, in that case.

DR. KALLOO: Do you know what proportion of patients were receiving medications, either H2 blockers or PPIs, for reflux?

DR. MacDONALD: They're trying to obtain that for you.

DR. KALLOO: Okay. Why don't we move on then. Thank you.

DR. STEINBACH: I think the adverse events are comparable to the other bariatric surgery, and, of course, patients should be warned that this is likely to happen.

DR. KOZAREK: Today I think they're also comparable, but can I ask one more question? Does this encapsulate? As somebody who studied the Angelchek anti-reflux device and wrote a number of manuscripts on it, one of the problems with that device is it encapsulated at the

EG junction, and it could erode six and eight and ten years later.

DR. MacDONALD: There is some--like with any foreign body, it is surrounded by tissue. I wouldn't call it encapsulated, though, like you're referring to. And, again, a major difference with this is that it's not supposed to be placed around the esophagus, which has no serosa, of course, and has other characteristics which most of us assume increase that rate of erosion. The band itself is implanted around a much thicker organ with a serosa, hopefully protecting that. Sutures are not placed directly between the device and the stomach, which also is known to increase erosion.

DR. KOZAREK: But it does play to the subsequent risk of erosion years down the line.

DR. MacDONALD: Yes, sir. There is an unquestionable risk of that.

DR. CHOBAN: I have a clarification before you leave. Was Actigol--

DR. MacDONALD: I'm not going to leave anymore.

[Laughter.]

DR. CHOBAN: Was Actigol used as part of the post-op protocol for more of the centers? Because I don't see a very high cholephysis.

DR. MacDONALD: No, ma'am. No, it was not.

DR. CHOBAN: Okay. The next question I have is, it looked like in the protocol that you all were using, at 36 months there was supposed to be an upper GI done again.

DR. MacDONALD: Yes.

DR. CHOBAN: And how many patients actually had that study completed, and what were the results of those?

DR. MacDONALD: Can you guys come up with that?

The protocol, of course, called for routine upper GIs at one year, so we do have--it was mentioned earlier that we didn't have that data. We do have that. And everybody that showed up for that visit, they had a routine upper GI obtained. So we have a large potential number of studies there to evaluate for whatever--

DR. KALLOO: Okay. While we're waiting on the data, let's--any other comments?

DR. CHOBAN: Okay. So at one year and three years would be--

DR. MacDONALD: Yes, ma'am.

DR. CHOBAN: And so the question I'd have is: Does the three-year data continue to support the one-year data given the concerns that were raised earlier regarding esophageal dilatation?

DR. MacDONALD: Right. We'll get that answer for you.

DR. CHOBAN: I guess coming back to providing--

sort of assuming that they all look dandy, I think that you are comparing rates that overall, while there's a lot of little things, there tends to be a lot of little things following open obesity surgery or the laparoscopic of the other two procedures. So in terms of the majority of the events that were discussed, I think they're pretty much in line with what the other therapies are.

DR. KALLOO: Dr. Talamini?

DR. TALAMINI: I agree that the complications are in line with the other operations. However, the benefits are not in line with the other operations. And as we talk about risk/benefit analysis of this operation, perhaps comparing it to others, although that's not specifically what we're here to do, I'm not sure that if the benefits re going to be less, then perhaps the complications ought to be less as well. We're talking about almost one in four of these patients in this study getting a second operation. That's a lot of patients. And I know that the explanation for that is different centers and different surgeons and different indications, but, still, the data is the data and it's one out of four. And that to me is concerning.

DR. NELSON: Now, this is from the meta-analysis, actually. It seems that the complication rates and reoperation rates reflect somewhat favorably on the LAP-BANDing, so we may have less benefit, but we also may have

less complications. So, again, that may be something we have to weigh.

I want to amplify earlier comments that the surgeons need to be well--I mean, that may speak to the learning curve of the surgeons, and that's something we will need to address later in the session perhaps, and, secondly, making sure that patients are informed that there are a number--even though this may be a "safe and effective" device, there are complications associated with it, and this is not just a walk in the park.

DR. KALLOO: Dr. Foote?

DR. FOOTE: I want to bring up another comment, something I had mentioned earlier about the slippage issue and the potential benefit of putting posterior sutures as a means to prevent the slippage issues. Is there any thought on doing a subset of patients with posterior sutures to see if these patients have a significantly lower incidence of slippage?

DR. O'BRIEN: None of the patients in the U.S. study had posterior fixation. It wasn't a part of the protocol. In the international study, it varied between centers.

It's been a part of my practice for most of the patients that I've treated. Almost all had a posterior fixation. It's one of a number of methods we use to prevent

the problem of prolapse. I think it's an important addition. It's not the only component, though. There are other things.

DR. FOOTE: Has anyone ever analyzed the data comparing the patients who had posterior sutures to those who did not to see if it did indeed significantly decrease the rate of slippage? The reason I'm bringing this up at this point is that that was a common cause of reoperation, and if you can address that by modifying the operation, then that would make it less morbid.

DR. O'BRIEN: No, I don't believe that has occurred. Other changes, though, that have occurred is a higher placement of the band, the aim being to get above the lesser sac, which should reduce the likelihood of slippage or prolapse. And there's also been better fixation anteriorly and laterally. And I think a combination of these plus good dietary advice, eating pattern after the operation has helped. And certainly the problem has very, very much reduced in my own practice, as I mentioned earlier, that there's just been two patients in the last 300 that have had a problem.

DR. KALLOO: Thank you.

Did you have a follow-up on the numbers?

DR. MacDONALD: I was just going to say, in the U.S. experience, as Dr. O'Brien said, that part of the

protocol wasn't posterior fixation, but I think most definitely with the expanded access study and with future instructions, that's going to be a big part, either to make sure--there's still no consensus as to what technique you should use, whether you go through the part that's flaccid or posteriorly where you don't even enter any free space, or whether or not you simply go lower and put in posterior sutures. That's still an issue which has to be resolved by comparative studies and literature and whatever.

DR. KALLOO: Okay. Thank you.

DR. HIRSCH: The very high rate of adverse events, 88 percent, I suppose a lot of this must be just learning to live with the band, that is, the nausea and vomiting that have come about, and people learn to accommodate that. I think that's why it works in the first place, so it almost isn't like an adverse event.

On the other hand, there are the more serious adverse events, and I would think this device has the advantage, at least, of being able to be taken down and removed more easily than the other procedures.

DR. BARANSKI: In comparing the adverse events with the international versus the U.S. study, the serious events are approximately, I think, about 40 percent. Is there any indication--in the international study dealing with more experienced surgeons after having done 50 have

reduced the serious events to somewhere around 40 percent. Is there indication that those are continuing to be reduced as time goes on?

DR. O'BRIEN: Yes, there is. We saw even from the U.S. study there's a progressive decrease of adverse events, also in the international study, also in my own experience. I think the peri-operative and early adverse events are very much reduced, and also the three late problems which we are concerned about are prolapse, erosion, and tubing breaks, and all of these seem to be decreasing in frequency.

DR. BARANSKI: Do you attribute that to any particular technique? Suturing was one of them, you said.

DR. O'BRIEN: Yes, certainly for the prolapse, which is the major problem, there's a number of items of technical change which we've instituted which we think make a big difference.

The tubing problem is corrected by more appropriate linear placement and the new device which became available the middle of last year. We expect that will become much less of a problem.

DR. BARANSKI: I believe that the--excuse me.

DR. O'BRIEN: Sorry. I'm not sure--this gives you a picture in my own patients of the decrease in problems with each cohort of 100 patients, where we had 30 prolapses in the first 100 patients, 26, 17, and 12. And then in the

last 300 patients, we've just had those two patients in the fifth hundred. So there is the appearance--there clearly is a time factor with this, and we will have more problems. But, nevertheless, calculating in the time factor, there is an improvement.

DR. KALLOO: Thank you.

Dr. Linner?

DR. LINNER: I think the complication rate is not too disturbing, with the exception, in my view, of the number of explants. I think there are 48 explants, and they were sort of generally over the period of the three years.

The contention is that the revision procedures after an explant are no more complication-prone than the original procedure, and I don't believe that. I think that there would be more complication in revisions.

The thing that does concern me, though, is the possibility of erosion, even though Dr. O'Brien mentions that they have done posterior suturing and anterior suturing, they haven't had it happen. I certainly don't deny his facts, but I think given this situation out over a large population of surgeons, it may become a problem.

Then the esophageal situation was mentioned by, I think it was Dr. Sugarman from Medical College of Virginia. I think that has to be pursued. Whenever you put a band around the lower esophagus or the upper stomach, I should

say, just below the lower esophagus, that is apt to pose a problem.

Regarding the port, an interesting thing. A woman who had had this operation done elsewhere came to our office. I wasn't there, but my associate saw her and she had had the procedure done, and she wanted something done at the port site to either remove or add saline. I don't know which it was. But, in any event, he declined to do it because he didn't want to take it on. Now, that could be a problem with transient populations, people moving around. They've got a port site, they'd like to get some of it out. How do you handle that?

DR. KALLOO: Do you have a response, by the way, to data that was asked by Dr. Choban? Do you have--

DR. KALLOO: The results of the upper GIs at 36 months, number of patients who have completed them and so far what the results are.

DR. MacDONALD: There were 213 upper GI studies at 12 months, 97 at 36 months. At 36 months, there were eight previous esophageal dilatations--the severity here is not yet available--that apparently were noted on a previous study, but were continuing to be stable. So apparently there were not any new ones, and I hesitate to say this because I don't know exactly yet. But apparently they weren't new but they were stable from previously noted

dilatations, and that's 8 out of 97.

DR. KALLOO: Thank you.

Dr. Talamini, will you summarize the panel's comments?

DR. SAWICKI: Can I ask a question before we summarize?

DR. KALLOO: Sure.

DR. SAWICKI: Can you comment on the esophageal dilatation for one minute about what you think the clinical significance of those are? You're following them and by and large you're not doing any kind of intervention? Am I summarizing that correctly? What's your impression? They're there. They bother you. You see them.

DR. MacDONALD: My personal opinion is that in a lot of cases they're transient. Because of the restriction by the band, you are going to see the esophagus ballooning out when that barium column comes down, stops for a little while, and then goes through, with the esophagus returning to normal.

Again, to me it shows that the band needs to be placed around the cardia of the stomach rather than the GE junction or esophagus, and I believe that strongly. You have to have a proximal gastric pouch. It's a gastric restrictive procedure not an esophageal restrictive procedure. And I think that has to be very strictly taught

to surgeons that you don't place it around the esophagus or the GE junction.

And I feel that when you do use that appropriate caveat in placing it that this is not going to be a major problem and result in some sort of surgical achalasia. Clearly, if it's already present and folks are getting a sigmoid esophagus, you need to follow it, either take out the band if that's indicated--you know, but clearly that's a problem that has to be followed in anybody that has it.

And if I were to have any, I would be following them much more carefully and probably get manometries and determine what was going on.

Does that answer your question?

DR. SAWICKI: It does.

DR. KALLOO: Thank you.

Dr. Talamini?

DR. TALAMINI: A lot has been said in that session, but I think we could summarize it by saying that the panel does not view the adverse events as reported to be excessive in this population of patients undergoing this type of surgery, but the panel raised three specific issues. One is what sounded like as yet unanswered technical issues regarding exact placement, number of sutures, where the suture should be. Number two is the issue of potential longer-term erosion of a prosthesis in this region beyond

even the six years that's been studied internationally. And number three, whether removal of this device affects future or subsequent anti-obesity operations in terms of technical ability and success of subsequent operations.

DR. KALLOO: Thank you. Question 5. Oh, Question 4, sorry. Data from the PMA and from the literature indicates that adverse events continue to occur beyond two years. Please discuss the adequacy of the two-year follow-up period and the need for additional safety data, either pre- or postmarketing.

DR. SAWICKI: I guess this is the billion dollar question. I think if I understand what's been presented today, the study has shown that within a two-year period, the weight loss begin to plateau or largely plateau, which shows that the efficacy is evident at that point.

What is unknown is where we are with regard to long-term sequelae, and that's a completely separate issue from efficacy. And for that reason, I do think that we need additional data. And then the next question is before or after approval.

I think that the safety of this device is at least comparable to other surgical measures for controlling obesity, and I think there are a few interventions and data that have shown that different interventions at a technical level will improve the safety. But I do think we need

additional data, and I think it would be reasonable to get that data postmarket.

DR. KALLOO: Diane?

MS. NEWMAN: I don't have anything more to add. I agree with him.

DR. KALLOO: Dr. Gabril?

DR. GABRIL: I agree with what he said, but I think we should get it premarket and longer safety data than postmarketing, I believe, because it's bothersome to have 54 percent of patients having symptoms beyond two years and 10 percent of them severe. It was proposed that most of the symptoms were due to a mechanical problem with the device, but how long should it take to correct that mechanical problem? Two years should be good enough to resolve the problems, I believe, and not to have any adverse events further. So the 10 percent being severe post two years is really bothersome, so probably that might persist. We don't know for how long. Therefore, I think premarketing, before we approve this, we should like to see the long-term follow-up with the adverse events, whether they improve or they stay the same or even progress.

DR. STEINBACH: I have nothing to add.

DR. KOZAREK: I would reiterate what I've already said, that these devices, if they've got a cocoon around them, can erode for years. So at a minimum, you're going to

need to have some kind of a postmarketing surveillance for five years and ten years.

DR. CHOBAN: I would agree with that. I think given the concerns of this esophageal dilatation issue being sort of--it seems fairly controversial among some of the different investigators. There seems to be fairly strong opinions on both sides of the fence that we don't see it at all and that it's a terrible thing. So that sort of leaves me a little concerned with what to do with that data.

I think that the dilatation from 2 centimeters to 3 centimeters may not be, you know, anything that anybody loses sleep over, but the air-fluid levels and mediastinums and the sigmoid esophaguses that have been shown at some of the recent meetings are very concerning. So I think to only have a third of the patients with those 36-month upper GIs completed, I think that given that there's a lot of other--that there's some pretty well established therapies available to these patients in the coming period of time, to get the 36-month data would probably be useful.

DR. KALLOO: Dr. Talamini?

DR. TALAMINI: I think the original study was designed for 36 months, and I think it would be good to have that 36-month data to really understand some of the issues. And I also agree that even with that data, the issue of erosion is going to have to be studied in postmarket--or

potential post-approval studies.

DR. NELSON: This must be the problem following a person who's the lead reviewer. I have nothing really new to add other than to amplify that it seems to me that the risk and the benefits were designed for assessment at 36 months, the benefits seem to be less than comparable strategies, the risks may increase--have been shown to increase after two years, and we probably need to have that follow-up data. The long-term five- or ten-year follow-up is also probably a good idea, and in the absence--if there were no other surgeries in the interim, there was not vertical banded gastroplasty or nothing else you could offer them in the interim, I would be pushed towards making this postmarket evaluation. But there are other alternatives, so I don't know why this--I guess I would say this could be done premarket.

DR. FOOTE: I agree with previous comments that looking at the data at three years premarket would be prudent.

DR. HIRSCH: I agree. I'm not so sure, by the way, that efficacy is because something happened in two or three years that we're sure that six and seven years, with this procedure the efficacy will be the same. So that's another matter.

But one of the reasons--one of the things I would

imagine is going to happen when this does become easily available, a lot of people are going to want it, because there's a huge public out there who desperately need some sort of help for obesity. And one of the reasons I'm for premarketing further analysis of that is to give those people who wish to make the selection of whether they want to do it or not all the information we can give them. It's all well and good for us to sit here and theorize as to what erosion might happen in six years or something. But you would like to give the people who are going to make this choice every opportunity to make an informed choice. And it seems to me that only by further premarketing analysis would we have the data to give them.

DR. BARANSKI: No further comment.

DR. LINNER: I think there should be at least a three-year follow-up for the development of these complications, and preferably five years. We have to remember that the foreign groups, foreign countries in this study, the European and Australian and so forth, the countries don't represent all of the European countries that are using this device. And many of the others who aren't as expert as they are--and they had 50 cases they did before they started. These other people are having more problems, not all of them, but there are reports in the literature of a higher incidence of erosion. There have been some deaths

reported in the literature. So we have to look at how this also is going to play with the average surgeon.

One other thing, I don't know how much control this group has, but I think it is very important that GI laparoscopic surgeons who don't have obesity surgery experience should not be doing this operation.

DR. KALLOO: Dr. Talamini, would you summarize--

DR. SAWICKI: Can I make one more comment on that?

DR. KALLOO: Sure.

DR. SAWICKI: I want to reamplify what Dr. Linner said about experience in using or performing bariatric surgery. I think that's critical if you expect to have a reasonable success rate.

But like you would rather not do bariatric surgery using the currently NIH-recommended procedures, I don't think that an inexperienced individual should ever consider using this device either. And I would be careful about drawing inferences from the literature from other groups who have had bad outcomes if you don't know the level of experience or training for those individuals.

I think it's critical to take the data presented today in light of what can be expected under optimum conditions, and I think we have to expect that the device will be used responsible by surgeons in this country.

DR. KALLOO: I think we're going to address

physician training a couple questions down the road. So, Dr. Talamini, will you summarize the comments?

DR. TALAMINI: Mr. Chairman, the committee's majority opinion is that the to-market follow-up is not adequate, and the majority opinion sounds as if they would prefer three-year data as the originally designed period.

DR. KALLOO: Okay. Question 5. The percent EWL and complication rates--example, band slippage/pouch dilatation, stoma obstructions, and reoperation counts--varied significantly by site. Please discuss the significance of site-to-site variation. Please discuss whether this variation could be related to a training issue, a patient selection issue, or some other reason.

DR. SAWICKI: I left my crystal ball at home.

This is really tough to answer. Clearly, there's a difference in terms of--especially for the weight loss, clearly, site-to-site variation. And whether this is a difference in patients, their diets, regional difference in diets, or the actual efficacy of the device or the way the surgeon places the device or the post-operative care for that center, it's really--without having that kind of control over the data in terms of diet, it's going to be very difficult to answer that question with any certainty. So I can't give a qualified answer to that without more data.

Is there more data regarding regional differences by site in terms of diet or technique?

DR. MacDONALD: No, there is not. The answer to the question simply is it's all the mentioned causes and more. So, yeah, it's selection, patient management issues, surgeon experience, and bias issues. So all those things are clearly involved.

DR. KALLOO: Thank you--

DR. MacDONALD: But as far as regional differences in diet and type of patients, I anecdotally don't believe there would be a reportable difference in any of that. But we don't have that data.

DR. KALLOO: Thank you.

Ms. Newman?

MS. NEWMAN: I agree. I think that there is a lot of unanswered questions. We're assuming that it may be a variation in learning curve of the surgeon, but it could be a patient selection issue. The European information was a retrospective chart review, so did they go through every patient that had it? We don't know that. Whereas, ours was prospective.

So it's hard--I just think we're comparing things without a lot of information, and if you can't pool that up, I don't know how we can base it on one individual variable.

DR. KALLOO: Dr. Gabril?

DR. GABRIL: No further comment.

DR. STEINBACH: I don't think we can say anything with no data.

DR. KOZAREK: Training, technique, patient belief. When we were debunking the gastric bubble and finally did the placebo controlled trials, if you have somebody who really believes in a technique, the patients believe in it. And it's the same thing with medication trials right now. You get some placebo controlled sites that get a 60 to 70 percent response to placebo. So it's probably a variety of all sorts of things, not that I'm saying that this is placebo.

DR. CHOBAN: Well, I guess I'd look at it in a little bit different way in that when I look at the centers where the investigational sites were, it really is kind of a who's who of the obesity surgery big guns in this country. And so I think patient selection is probably extra-ordinarily, to a point, pretty uniform. These are people who have had a lot of experience with previous obesity surgery, and I think the problem is there isn't one thing that will predict who is going to be the success group and who's not going to be the success group.

So within this group of highly experienced people, then the answer is, well, not everybody was laparoscopic surgeons. Well, you got one of the centers who's one of the

huge guns in laparoscopic gastric bypass, talk about advanced laparoscopic skills. So I'm not sure that that's something you can just say, oh, that was the problem.

And my concern would be, if you take what I think is really a pretty tight group and now we put it out through the country that, if anything, we're going to see greater diversity from center to center. So whether you can fix that by training, I don't know.

DR. TALAMINI: That's exactly the point I was going to make. If we see this kind of variation among obesity surgeons who are good and know exactly what they're doing in this field, just wait until this is out in the general public and we get that spread that I talked about.

I believe that most of the variation probably is surgeon- and clinical practice-oriented. It sounds like some of these groups were pulling these things earlier for--you know, because that was their bias in some sense.

DR. CHOBAN: Can I request one quick clarification? In terms of the centers and in terms of what the dietary recommendations were for patients post-operatively, was it mainly extrapolating from what you had usually done in your practice before then so each center had their little ways they did it? Or was there a pretty tight protocol for this?

DR. MacDONALD: No, it was--while there was one

instruction booklet passed out as part of the educational material, pretty much I think each center what they generally do with their individual patients. And there's a little bit of variations. Some were on liquids longer before they advanced and, of course, there's a lot of variation on how you give instructions of that complexity. So there was a lot of differences.

DR. KALLOO: Thank you.

DR. NELSON: No additional comments.

DR. FOOTE: No additional comments.

DR. HIRSCH: Nothing to add.

DR. BARANSKI: In the information that's provided to the surgeon, I noticed there were no guidelines regarding the amount of fluid that is infused to restrict the lumen or make the lumen larger. The only thing I saw there was 24 cc's related to so many millimeters. Do you have a baseline criteria, and is the amount of restriction in the lumen related to the slippage?

DR. MacDONALD: You're right. In what you read there wasn't any specific instructions about how much to leave in. It was communicated during--as these slippages began to be noted, it was communicated to leave the band empty. We used to leave 1 cc in when it was implanted. Then it was decided to try and leave it empty to allow the band to scar in some before adding, because, clearly,

constricting the lumen by adding saline to the band was a key factor in slippage. And they generally did not occur until you started narrowing down that stoma size. So as that was a key factor, we didn't usually start adjusting until four to six weeks after surgery to try to allow some scarring in to prevent that.

DR. BARANSKI: Do you have a scale whereby so much infusion gives you so much restriction of lumen and so forth?

DR. MacDONALD: I can tell you anecdotally that I doubt that that would be possible because there's so much variation in thickness of the stomach and how much tissue you have around it that it's very--some people would have a very small lumen with 1 cc, whereas some patients would take 4 cc's. So there's an awful lot of individual variation.

One of the big differences, I think, in the European and the U.S. experience is that the Europeans adjust much more frequently at smaller intervals. I think that's becoming known to be the best way to do it. Whereas, in the U.S. you would try to just put as much as in you could, get it to its endpoint, and I don't think that's the way to manage the band. So there was a large amount of learning going on just about that small part of the management.

DR. O'BRIEN: The common protocol which we follow

is to add no fluid until the seventh week after placement of the band. We then add 2 ml, and then we see the patient every month, and we assess their progress, and we add 0.3 of a ml at each new consultation if we want to progress further. We normally find that in the first year we would adjust the band about six times. Usually by then we've found a level which is about correct, and the commonest area is around 3, 3.5 ml, not to commonly above 4 ml, but it varies a lot between patients. But it enables us to gently find a level that's correct to get a weight loss without getting any symptoms of distress.

DR. CHOBAN: Could I has for--just the band, we were seeing a 10 percent weight loss as three weeks. You get a 10 percent weight loss with a band uninflated.

DR. O'BRIEN: That's right.

DR. CHOBAN: Is that a correct interpretation?

DR. O'BRIEN: Yes. The most important reason why the band works is not because it creates a mechanical block, but it actually takes away appetite. People's focus on food moves lateral, and so that works very well initially. And then by adding more fluid, it reinforces it. We get very good weight loss in that first seven weeks before we've even added fluid.

DR. KALLOO: Okay. Thank you--Dr. Linner?

DR. LINNER: I don't have much to add. I think

it's a learning curve thing. You have to remember the international study, they all had 50 cases before they even started the study, and here they started from the get-go. And that's the variation, in my opinion.

DR. KALLOO: Dr. Talamini, could you summarize?

DR. TALAMINI: I think the panel's opinion is that it's impossible to tell the exact cause of the site-to-site variation based upon the options proffered in the question, but that the variation is reflective of what may occur in the country as a whole post-approval.

DR. KALLOO: Before we continue, we are going to take a short 5-minute break. Five minutes, because we have a lot to do. Thank you.

[Recess.]

DR. KALLOO: The next question--I guess our AV person is gone.

Question 6, if we may continue: In addition to the U.S. study, the submission provided results from a retrospective international study and a literature review. Please discuss the contribution of these studies in supporting the safety and effectiveness of the LAP-BAND system device.

Dr. Sawicki?

DR. SAWICKI: I think to a large extent those studies are helpful in that they reassure me that the

relatively short study presented that was prospective has data that's in line with the more extensive other studies. And in that regard, I think they're very helpful in reassuring me that this is not a small sample of patients who have results that are unique and only expand the study, that the data will fall off in other directions.

I'm also reassured by some of the data presented from the international study showing that certain problems are dropping off with time and experience, and I think that's also reassuring in that we can expect that there's a learning curve with this procedure and that the outcomes will be better with time.

I don't think that they show any deficits that are new or different from the U.S. study.

DR. GABRIL: I think this data was helpful in that it provide three important points. One is we have data now on sustained weight loss beyond two years based on this study. It also provided information on improvement of comorbidity. And the third point was the rate of the band prolapse was much lower in the European study than the U.S. study, which might be attributed to the experience of the surgeons.

DR. STEINBACH: I think the literature review is important because it shows that although the severe complications may be less through the LAP-BAND, the

effectiveness is not the maximum possible of known techniques.

DR. KALLOO: Ms. Newman, do you want to comment on Question 6?

MS. NEWMAN: I think they were helpful. It's just that--I think they were helpful in helping us review the LAP-BAND.

DR. KALLOO: Dr. Choban?

DR. CHOBAN: I also think they were helpful in terms of, again, helping point out what well may be the learning curve issues.

I think the effectiveness does seem to be significantly greater in the international study than in the U.S. study, so I don't know if that's going to be something that also improves as the learning curve improves, or it does sort of raise the question, though, is there something different in the two populations at that point.

DR. TALAMINI: Pass.

DR. NELSON: With obvious limitations, the international study is retrospective, but it tends to be more favorable. I would suspect that the smaller U.S. data would probably be more generalizable to the U.S. experience once it expands, as Mark has already pointed out, that people were starting at LAP-BAND zero in the U.S. study and starting at LAP-BAND 50 in the international study, and that